AWARD NUMBER: W81XWH-15-1-0605

TITLE: Prevention of Posttraumatic Contractures with Ketotifen (PERK)

PRINCIPAL INVESTIGATOR: Kevin Hildebrand

CONTRACTING ORGANIZATION: University of Calgary
Calgary, T2N1N4

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TYPE OF REPORT: Annual Report

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Fort Detrick, Maryland 21702-5012

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University of Calgary
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14. ABSTRACT

Fourteen sites across North America have been identified to conduct a randomized clinical trial. A trial design of a multicentre, multidose, placebo controlled in elbow fracture patients was developed. An unsuccessful operating grant application to the Canadian Institutes of Health Research was completed. A Preapplication to the Peer Reviewed Orthopaedic Research Program (PRORP) Clinical Trial Award (CTA), W81XWH-16-PRORP-CTA, was submitted. Database development and Pre-IND consultation were completed.

15. SUBJECT TERMS

Post-traumatic contractures, Randomized Clinical Trial, Elbow fractures, Multicentre, Operating grant applications, PRORP Clinical Trial Award application

16. SECURITY CLASSIFICATION OF:			17. LIMITATION OF ABSTRACT	18. NUMBER OF PAGES	19a. NAME OF RESPONSIBLE PERSON
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1. INTRODUCTION

This Clinical Trial Development Award (CTDA) pertains to the FY14 Peer Reviewed Orthopaedic Research Program (PRORP) Clinical Trial Development Award (CTDA) announcement to identify and reduce secondary health effects (e.g., joint contracture) that follow reduced mobility from traumatic neuromusculoskeletal injury. This CTDA facilitates an opportunity to design a Phase III RCT on the use of ketotifen in post-traumatic joint contractures. The goal is to design and develop the infrastructure to complete a multicenter Phase III RCT. This will facilitate applications for operation funds to complete the Phase III RCT. The identified funding mechanisms are PRORP or Peer Reviewed Medical Research Program (PRMRP) Clinical Trial Award (CTA) competitions and the Canadian Institutes of Health Research (CIHR) for the Phase III RCT.

2. KEYWORDS

Post-traumatic contractures, elbow fractures, randomized clinical trial, multicenter, ketotifen, placebo, IND application, data base, training, contracts, institutional review board.

3. ACCOMPLISHMENTS

What were the major goals of the project?

Development of Phase III RCT	Timeline	Status
Major Task 1 Recruit Sites	Months	
Present at American Society for Surgery of the Hand September 2015 in Seattle	0	Completed
Present at Canadian Orthopaedic Trauma Society Meeting at the annual Orthopaedic Trauma Association meeting October 2015 San Diego	1	Completed
Present at Major Extremity Trauma Research Consortium Fall 2015 – Winter 2016.	4-6	Cancelled
Contact US Military Organizations	1-6	Completed
Site Investigator and Site Research Coordinator training	9-15	Pending
IRB and contract completion	12-18	Pending
USAMRMC HRPO review and approval	12-18	Pending
Major Task 2 Regulatory Applications	Months	
Pre-IND Consultation	1-3	completed
IND Application Completion	4-6	In Progress – 40% complete
FDA review, Response to clarification requests or questions	7-9	Pending
Major Task 3 Medication Packaging and Distribution	Months	
Identify Manufacturer Canada and US	1-3	Completed
Identify Distributor Canada and US	1-3	Completed

Finalize manufacture and distribution plan with research design / Clinical Research Unit	15-18	Pending
Major Task 4 Data management and Safety	Months	
Identify database and partner – Clinical Research Unit	1-2	Completed
Develop Case Report Forms, consent forms	6-12	Case report forms completed, consent forms pending – 80% completed
Develop database and multicenter submission process	12-18	In progress, 30% completed
Develop Xray acquisition and Archiving system	12-18	In Progress, 60% complete
License for patient reported outcome measures	15-18	Pending
Data monitoring / Quality Assurance plan	15-18	Pending
DSMB establishment	15-18	Pending
Major Task 5 Phase III RCT design		
Study design, Sample size calculation, Statistical analysis plan	6-18	Completed
Confounding variable analysis	12	Completed
Major Task 6 Transition Plan		
Phase III RCT design – sample size calculation, statistical analysis plan, outcome measure and confounding variable analysis	6-18	Completed
Phase III RCT Grant writing – PRORP or PRMRP CTA; CIHR	6-18	In Progress, 30% complete
Public Communication – AHS communication, local media Calgary	15-18	Pending

What was accomplished under these goals?

The major activities achieved include identifying participating sites for the multicenter randomized clinical trial (RCT); developing a Phase III RCT study design; applying to operating grant opportunities for the Phase III RCT from the CIHR and PRORP; identifying a medication acquisition, packaging and distribution solution for ketotifen and placebo; ascertaining a system to acquire, archive, and analyze radiographs from the sites that respects privacy considerations and will interact with our data collection; developing a study / project management (randomization, exchange of data in an FDA compliant manner), and an on-site and distance monitoring process; and regulatory applications for ketotifen use in post-traumatic contractures.

A total of 14 sites across North America have been identified – 11 in Canada and 3 in the US (Major Task 1). Two of the US sites are part of the Major Extremity Trauma Research Consortium (METRC). The METRC sites are hospitals that manage civilian and military populations. The 14 sites provide access to sufficient numbers of patients to complete the multicenter RCT trial design. These sites were identified through the

presentations at the American Society for Surgery of the Hand (ASSH), the Canadian Orthopaedic Trauma Society (COTS), and contacting US military organizations, and a formal presentation to METRC was not required.

Operating grants were submitted to 2 agencies (Major Task 6). An unsuccessful application was sent to the CIHR 1st Live Pilot Project Scheme operating grant funding opportunity March 2016. A preapplication was submitted September 7, 2016 (Log No. OR160026) to the PRORP CTA announcement W81XWH-16-PRORP-CTA. We were invited in mid October 2016 to submit a full application to this announcement.

In the course of writing these applications, several other tasks were completed. The Bay Area Research Logistics (BARL) of Hamilton, Ontario was engaged to manufacture and distribute the medications (Major Task 3). Finalization of the plan is pending, and will be solidified once a source of funding is obtained for the Phase III RCT. The Clinical Research Unit (CRU) at the Cumming School of Medicine at the University of Calgary has been engaged as the data management center and will provide logistical support for conducting the trial (randomization, coordinating distribution with BARL). The Calgary Image Processing and Analysis Centre (CIPAC) will provide image archiving and interpretation for the multicenter RCT. Further work is required on the data base development, imaging acquisition, and consent forms. These are all part of Major Task 4. Writing the operating grants facilitated the design of the Phase III multicenter RCT (Major Task 5). Ketotifen is an oral anti-asthmatic medication and a topic ophthalmic agent for the treatment of allergic conjunctivitis. An FDA IND application is required to use it in post-traumatic joint contracture prevention. The Division of Pulmonary, Allergy, and Rheumatology products is the FDA branch identified for the application and we have consulted with their Center for Drug Evaluation and Research (CDER) contact, Sandy Barnes. We are now working on the IND application (Major Task 2).

What opportunities for training and professional development has the project provided?

Nothing to Report.

How were the results disseminated to communities of interest?

The major reporting activities were the presentations at the ASSH and COTS meetings. The goal was to invite participation in the future Phase III multicenter RCT and to provide input into the design of the RCT.

What do we plan to do during the next reporting period to accomplish the goals?

There are other components of the CTDA yet to complete. For Major Task 1 application for USAMRMC HRPO review and approval will be completed. The remaining aspects include training of the site Principal Investigator (PI) and Research coordinator and applications to each of the sites Institutional Review Board (IRB). These are pending confirmation of successful applications for the operating funds to conduct the Phase III multicenter RCT. In Major Task 4, licenses will be obtained for the Oxford Elbow Score (OES) and the Disabilities Arm, Shoulder, Hand (DASH). The FDA application will be completed (Major Task 2). Logistics around the medication and, data and project management including Xrays, will occur. The full application to the PRORP

CTA to fund the Phase III multicenter RCT will be submitted. An application to the Project Scheme of CIHR will be submitted late Spring / Summer 2017.

4. IMPACT

What was the impact on the development of the principal discipline(s) of the report?

Nothing to report.

What was the impact on other disciplines?

Nothing to report.

What was the impact on technology transfer?

Nothing to report.

What was the impact on society beyond science and technology?

Nothing to report.

5. CHANGES/PROBLEMS

Changes in approach and reasons for change

Nothing to report.

Actual or anticipated problems or delays and actions or plans to resolve them

No problems in the current reporting period. The anticipated implementation of a successful application to the PRORP CTA is October 1, 2017 at the earliest. The current CTDA ends March 29, 2017. Major components yet to achieve are training of the site personnel. It is the opinion of the investigators that this training should occur close to the time of implementation of the Phase II RCT. Thus, an application for a 1 year no cost extension will be submitted to the Awarding Agency Grants Officer. Finalization of the medication distribution, data and project management logistics, appointing members of the Data Safety and Monitoring Board and applications for REB approval at each site will wait pending notification of a successful operating grant application.

Changes that had a significant impact on expenditures

Expenditures are much lower than anticipated. This relates to the delay in the plans for site personnel training and the application to the IRBs.

Significant changes in the use or care of human subjects, vertebrate animals, biohazards, and / or select agents

Not applicable. None of these considerations are relevant to the CTDA.

6. PRODUCTS

Publications, conference papers, presentations

Nothing to report.

Website(s) or Internet site(s)

Nothing to report.

Technologies or techniques
Nothing to report.

Inventions, patent applications, and / or licenses
Nothing to report.

Other Products
Nothing to report.

7. PARTICIPANTS & OTHER COLLABORATING ORGANIZATIONS

What individuals have worked on the project?

Name:	Kevin Hildebrand
Project Role:	Principal Investigator
Research Identifier:	orcid.org/0000-0001-8786-9021
Nearest Person Month worked:	2
Contribution to Project:	Overall management. Writing grants, study design. Recruiting sites. Obtaining data management, medication partners.
Funding Support:	Department of Surgery University of Calgary

Name:	Alex Garven
Project Role:	Research Coordinator
Research Identifier:	None
Nearest Person Month worked:	3
Contribution to Project:	Regulatory application (IND). Database development. Case report forms, consent. Assist in study design and writing grants.
Funding Support:	Partial support from Worker's Compensation Board of Alberta, Division of Orthopaedic Surgery, University of Calgary.

Has there been a change in the active support of the PD/PI(s) or senior / key personnel since the last reporting period?
Nothing to report.

What other organizations were involved as partners?
Nothing to report.

8. SPECIAL REPORTING REQUIREMENTS

COLLABORATIVE AWARDS
Nothing to report.

QUAD CHARTS
Year 1 Quarter 4 quad chart is included in the appendices.

9. APPENDICES

A. Quad Chart
B. CIHR application Unsuccessful Notice
C. Invitation Full Application

Prevention of Posttraumatic Contractures with Ketotifen (PERK)

OR140142
W81XWH-15-1-0605

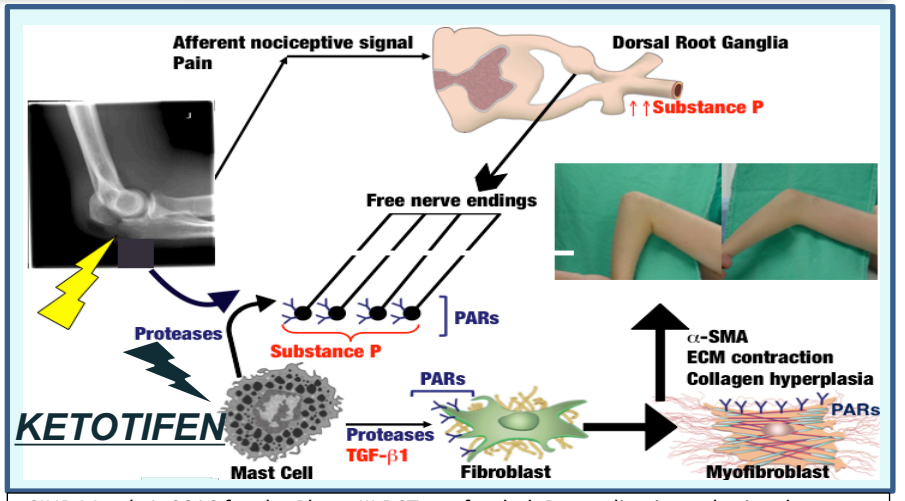
PI: Kevin A. Hildebrand **Org:** University of Calgary **Award Amount:** $238,420

Study/Product Aim(s)

- Major Task 1 – Recruit sites
- Major Task 2 – Regulatory applications
- Major Task 3 – Medication Packaging & Distribution
- Major Task 4 – Data Management and Safety
- Major Task 5 – Phase III RCT design
- Major Task 6 – Transition Plan

Approach

This is a clinical trial development award. The goal is to design and develop the infrastructure to complete a multicenter Phase III RCT. This will set the stage to apply to PRORP or PRMRP Clinical Trial Award competition. Applications will also be sent out to the Canadian Institutes of Health Research (CIHR) for the Phase III RCT.



CIHR March 1, 2016 for the Phase III RCT not funded. Preapplication submitted to opportunity W81XWH-16-PRORP-CTA. Further refinement of REDCap database. Sponsoring branch of FDA consulted and start of IND application.

Timeline and Cost

Activities CY	15	16	17	
PRORP-CTA preapplication				
March 2016 CIHR grant				
IND application				
Data Management and Safety				
Estimated Budget ($K)	**$19**	**$208**	**$11**	**$000**

Updated: (January 10, 2017)

Goals/Milestones

CY16 Goal – PRORP-CTA
☑ Preapplication submitted September 7
CY16 Goals – Submit Grants for Phase III trial (Transition)
☑ CIHR – Unsuccessful
CY16 Goal – IND
☑FDA branch identified and application started
CY16 Goal – Data management and Safety
☑ Development of CRF
☑ Trial runs of Database completed

Comments/Challenges/Issues/Concerns

- None

Budget Expenditure to Date

Projected Expenditure:$216,280
Actual Expenditure: $18,298

CIHR IRSC

Institute of Aboriginal Peoples' Health
Institute of Aging
Institute of Cancer Research
Institute of Circulatory and Respiratory Health
Institute of Gender and Health
Institute of Genetics
Institute of Health Services and Policy Research
Institute of Human Development and Child and Youth Health
Institute of Infection and Immunity
Institute of Musculoskeletal Health and Arthritis
Institute of Neurosciences, Mental Health and Addiction
Institute of Nutrition, Metabolism and Diabetes
Institute of Population and Public Health

Institut de la santé des Autochtones
Institut du vieillissement
Institut du cancer
Institut de la santé circulatoire et respiratoire
Institut de la santé des femmes et des hommes
Institut de génétique
Institut des services et des politiques de la santé
Institut du développement et de la santé des enfants et des adolescents
Institut des maladies infectieuses et immunitaires
Institut de l'appareil locomoteur et de l'arthrite
Institut des neurosciences, de la santé mentale et des toxicomanies
Institut de la nutrition, du métabolisme et du diabète
Institut de la santé publique et des populations

July 15, 2016

Dr. Kevin Arnold Hildebrand
University of Calgary
Cumming School of Medicine
Department of Surgery
Division of Orthopaedic Surgery
3280 Hospital Drive NW
Calgary, Alberta T2N 4Z6

Dear Dr. Hildebrand,

Your recent application to the Project Grant – Spring 2016 competition, entitled "PrEvention of post-traumatic contractuRes with Ketotifen (PERK)", has been considered by the Canadian Institutes of Health Research (CIHR). Unfortunately, your application was not approved for funding.

Your application reviews and competition results can be accessed through ResearchNet. If you are unable to view these documents, please contact us at support@cihr-irsc.gc.ca.

As CIHR does not notify co-applicants of the decision, we ask that you inform those individuals involved, along with their research institutions (if different from your own) of the outcome of this application.

Should you have any questions, please do not hesitate to communicate with a Processing Officer in the CIHR Contact Centre at 613-954-1968 or by e-mail at support@cihr-irsc.gc.ca.

Sincerely,

Martine Lafrance

Martine Lafrance, Ph.D.
Manager, Project Grant Program/Investigator Initiated Research Branch
Research, Knowledge Translation and Ethics Portfolio

432865-201603PJT-PJT-366152-48954-DLPNA

REPLY TO
ATTENTION OF

Assistance Agreements Group

Kevin Hildebrand
University of Calgary
3280 Hospital Drive NW
Calgary, AB T2N 4Z6
Canada
hildebrk@ucalgary.ca

RE: OR160026 - "Prevention of Post-Traumatic Contractures with Ketotifen II (PERK II)"

STATUS: INVITED TO SUBMIT AN APPLICATION

Dear Kevin Hildebrand:

You are invited to submit an application for a Fiscal Year 2016 (FY16) Department of Defense Peer Reviewed Orthopaedic Research Program (PRORP) Clinical Trial Award.

Your application must include the requisite components, comply with required preparation instructions, and be submitted by 11:59 p.m. Eastern time on December 7, 2016, as described in the FY16 PRORP Clinical Trial Award Program Announcement and General Application Instructions. **Applications must be submitted by the Authorized Organizational Representative through Grants.gov (www.grants.gov).** For synopsis details, full program announcement, and application package including instructions, go to http://www.grants.gov/web/grants/search-grants.html and enter Funding Opportunity Number W81XWH-16-PRORP-CTA under "Basic Search Criteria." The program announcement is located under "Related Documents," and the application package, including instructions, is located under "Package."

Please note that this invitation to submit an application does not assure funding.

Sincerely,

Teresa M. Parker Reeser
Grants Officer

cc: Melissa Green Parker, Ph.D.
PRORP, Program Manager